Spinal Dural Arteriovenous Fistulas Are Not Associated With Prothrombotic Factors

K. Jellema, MD; C.C. Tijssen, MD, PhD; R. Fijnheer, MD, PhD; P.G. de Groot, PhD; P.J. Koudstaal, MD, PhD; J. van Gijn, MD, FRCP

Background and Purpose—The cause of spinal dural arteriovenous fistulas (SDAVF) is unknown. In intracranial dural arteriovenous fistulas, an association with factor V Leiden mutation has been found. Therefore, we studied the association between prothrombotic factors and SDAVF.

Methods—Factor V Leiden mutation, factor II mutation, protein S, protein C, factor VIII, von Willebrand factor, and lupus anticoagulant were determined by means of standard laboratory tests in 40 patients and 119 control subjects matched for sex and age.

Results—Factor V Leiden mutation was not found in the patient group and was found twice in the control group. Factor II mutation was found in 1 patient and in none of the control subjects. There was no decreased activity of protein S, protein C, factor VIII, von Willebrand factor, or antithrombin III in patients in comparison with controls. Lupus anticoagulant was not found in the patient group and once in the control subjects.

Conclusions—We conclude that it is unlikely that prothrombotic factors are involved in the pathogenesis of spinal dural arteriovenous fistulas, but subtle associations are not ruled out. (Stroke. 2004;35:2069-2071.)

Key Words: arteriovenous fistula ■ spinal cord ■ thrombophilia

The cause of spinal dural arteriovenous fistulas (SDAVF) is unknown. Infection and trauma are among the factors that have been proposed as possible factors in the course of events leading to this condition. In intracranial dural arteriovenous fistulas, an association with factor V Leiden mutation has been found, whereas venous (sinus) thrombosis has also been implicated in the pathogenesis of that condition. Because of the similarities between cerebral and spinal fistulas, thrombophilia might also operate in patients with SDAVF. Therefore, we investigated the association between prothrombotic factors and SDAVF.

Patients and Methods

Between 1990 and 2002, 68 patients had SDAVF diagnosed and treated in the 4 hospitals mentioned in this article. Of these 68 patients, 12 had died (5 from cardiovascular disease, 2 from cancer, 2 from pneumonia, and 3 from unknown causes). Of the 56 survivors, 3 patients could not be traced, 4 patients did not respond, and 7 refused to participate in the study. In 2 patients no blood could be drawn. In 1 patient who died of an unknown cause, the medical history revealed pulmonary embolism; the medical history did not contain information about presence or absence of prothrombotic factors. The patient characteristics of the 28 patients who did not participate in this study did not differ from those of the 40 patients who participated.

The 40 patients were included in the current study between May and July 2002. The diagnosis of SDAVF was confirmed by angiography in all patients. From the medical records, we collected information on medical history, clinical features, time to diagnosis, and level of fistula. The clinical features of these patients have been described in more detail in a previous article. The patients had been treated in the Elisabeth Hospital Tilburg (16 patients), University Medical Center Utrecht (10 patients), Erasmus Medical Center (9 patients), and the Academic Medical Center in Amsterdam (5 patients). There were 36 men and 4 women. For each patient, 3 control subjects matched for age (±3 years) and sex were recruited (Sanquin Blood Bank, Utrecht, the Netherlands). The maximum age of control subjects was 70 years, because the blood bank does not accept donors older than age 70. In 1 female control, the blood sample was lost; hence, samples of 119 controls were obtained. All individuals gave their informed consent. Standard laboratory procedures were used for the following tests: activated protein C ratio, protein C activity, von Willebrand factor, lupus anticoagulant (Behring Coagulation System, Dade Behring Inc), factor VIII, antithrombin III (STA, Diagnostica Stago), and protein S with the use of an enzyme-linked immunosorbent assay. The factor V Leiden mutation was determined only if the activated protein C ratio was abnormal. Factor II mutation was determined according to a technique as previously described. The study protocol was approved by the institutional review boards.

We calculated the number of patients needed to detect a significant increase in the prevalence of factor V Leiden. The significance level was set at 0.05 and power at 0.8. The frequency of factor V Leiden in the normal population was set at 5%, whereas the possible
Table: Mean Age and Results of Laboratory Tests in 40 Patients With a Spinal Dural Arteriovenous Fistula and 119 Healthy Controls

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=40)</th>
<th>Controls (n=119)</th>
<th>Significance Level (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>62±9</td>
<td>60±8</td>
<td>0.229</td>
</tr>
<tr>
<td>Sex ratio, M:F</td>
<td>36:4</td>
<td>108:11</td>
<td></td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>1</td>
<td>0</td>
<td>0.252</td>
</tr>
<tr>
<td>Factor V Leiden mutation</td>
<td>0 2*</td>
<td></td>
<td>0.559</td>
</tr>
<tr>
<td>Factor II</td>
<td>1</td>
<td>0</td>
<td>0.252</td>
</tr>
<tr>
<td>Protein S†</td>
<td>115±18†</td>
<td>107±21</td>
<td>0.243</td>
</tr>
<tr>
<td>Protein C†</td>
<td>107±21†</td>
<td>97±18</td>
<td>0.066</td>
</tr>
<tr>
<td>Factor VIII†‡</td>
<td>105±49</td>
<td>112±39</td>
<td>0.399</td>
</tr>
<tr>
<td>von Willebrand factor†</td>
<td>104±38</td>
<td>106±32</td>
<td>0.761</td>
</tr>
<tr>
<td>Antithrombin III†‡</td>
<td>111±11</td>
<td>102±8.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>0</td>
<td>1§</td>
<td>0.748</td>
</tr>
</tbody>
</table>

*Both controls were heterozygous for factor V Leiden mutation.
†Relative activity (in %) compared to a normal plasma pool (set at 100%).
‡Two patients were treated with oral anticoagulants.
§Lupus anticoagulant was weakly positive in 1 control subject.
M indicates male; F, female.

In summary, our results suggest that it is unlikely that prothrombotic factors are involved in the pathogenesis of son with controls. There was even a greater activity of antithrombin III in patients, on average, than in controls. Lupus anticoagulant was not found in the patient group and was found once in the control subjects.

Discussion

In this study we could not demonstrate an association with prothrombotic factors in 40 patients with SDAVF. Also, the medical histories of the 40 patients were not suggestive of an increased risk of venous thrombosis. Only 1 of the 40 patients (who proved to have a factor II mutation) was known with a history of deep vein thrombosis and subsequent pulmonary embolism. The increased activity in antithrombin III in patients as compared with controls does not, to the best of our knowledge, have clinical implications. Decreased, but not increased, activity of antithrombin III is known to be a prothrombotic factor.

In cerebral dural arteriovenous fistulas, an association with venous sinus thrombosis has been described. Five of 22 patients were heterozygous for factor V Leiden mutation. Two of these patients had a history of sinus thrombosis, and 2 had a history of deep venous thrombosis. It was therefore speculated that physiological arteriovenous shunts of the dura mater may become pathological shunts after formation and (partial) recanalization of cerebral sinus thrombosis. Physiological arteriovenous shunts have also been described between lumbosacral radicular arteries and veins. We conclude from this study that the formation of a pathological shunt in spinal fistulas is not likely to be caused by venous thrombosis. Other factors should account for the formation of pathological shunts between a radicular artery and its corresponding vein. SDAVF is probably unable to account for these shunts, and the SDAVF still remains a mystery. Why does the disease strike men 4 to 5 times more often than women? Is it because of differences in anatomy, lifestyle, or hormonal factors? Why does SDAVF typically occur in middle-aged patients? Is it a cardiovascular disease with the same risk factors as for stroke or myocardial infarction? And why is the midthoracic spinal cord affected far more often than the cervical spinal cord? If trauma is a causal factor, why does SDAVF seldom occur in the most mobile part of the vertebral column, ie, the cervical spine? These questions warrant further research on the vascular anatomy of the spinal cord.

The retrospective design of this study has inherent shortcomings. The results in this study may underestimate the number of prothrombotic factors in the patients with SDAVF who did not participate. Some of these patients died of cardiovascular disease and unknown causes. A number of these patients may have had thrombophilia. However, because the medical records reported pulmonary embolism in only 1 patient, it seems unlikely that thrombophilia was highly prevalent in the nonparticipating patients.

In summary, our results suggest that it is unlikely that prothrombotic factors are involved in the pathogenesis of frequency of factor V Leiden in patients was estimated to be 22% (5 of 22 patients with factor V Leiden in cerebral fistulas in a previous study). For each patient, 3 controls were used. The total number of patients required to detect a significant increase in factor V Leiden was 43.

For statistical analysis, Fisher exact test was used to examine whether there was a difference in occurrence of factor V Leiden mutations, factor II mutations, and lupus anticoagulant between patients and controls. Other factors were analyzed by means of the independent t test (SPSS 10.0.5 for windows).

Results

The mean age in the patient group was 62 years (SD±9); in the control group, this was 60 years (SD±8) (Table). This difference was not statistically significant (P=0.229).

The median time to diagnosis was 15.5 months. Most fistulas were located in the midthoracic region. One patient had 2 fistulas: 1 at T8 and 1 at L3. Initial symptoms consisted of gait disturbances, leg numbness, and paresthesias. Symptoms at the time of diagnosis included micturition disturbances, weakness in 1 or both legs, and sensory disturbances.

Two patients and no control subjects were treated with oral anticoagulants (coumadin derivatives) at the time of study.

Activated protein C resistance was not found in the patient group and was found twice in the control subjects (P=0.559). Both controls proved to be heterozygous for factor V Leiden mutations. In 1 patient there was a factor II mutation; the medical history revealed that in the past he had deep vein thrombosis with subsequent pulmonary embolism. No controls were found with a factor II mutation. In no other patients or controls did deep vein thrombosis or pulmonary embolism occur.

There was no decreased activity of protein S, protein C, factor VIII, or von Willebrand factor in patients in compari-
spinal dural arteriovenous fistulas, but subtle associations are not completely ruled out.

Acknowledgments
We acknowledge the Janivo Foundation, Zeist, the Netherlands, for the funding of the current study.

References
1. Foix CH, Alajouanine TH. La Myélite nécrotique subaiguë. Rev Neurol. 1926;46;1–42. In French.
Spinal Dural Arteriovenous Fistulas Are Not Associated With Prothrombotic Factors

Stroke. 2004;35:2069-2071; originally published online July 1, 2004;
doi: 10.1161/01.STR.0000135766.22285.dc
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/35/9/2069

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office.
Once the online version of the published article for which permission is being requested is located, click
Request Permissions in the middle column of the Web page under Services. Further information about this
process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/